REVIEW

Effects of ventricular resynchronization in previously paced patients developing refractory heart failure

Résultats de la resynchronisation ventriculaire chez les patients déjà implantés d’un stimulateur cardiaque et en insuffisance cardiaque réfractaire

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Summary Biventricular resynchronization has been shown to be beneficial on morbidity and mortality in patients with symptomatic (NYHA class III or IV) systolic heart failure (left ventricular ejection fraction or LVEF is less or equal to 35%) under optimal medical treatment with electrical asynchrony (QRS ≥ 120 ms) and in sinus rhythm. The purpose of this study was to evaluate the efficacy and safety of upgrading to biventricular resynchronization in paced patients presenting with symptomatic systolic heart failure. Over a period of eight years, 24 paced patients with symptomatic (class III or IV) systolic heart failure (LVEF ≤ 35%) with electrical asynchrony (QRS ≥ 160 ms) received an additional left ventricular pacing lead and a biventricular pulse generator. We compared the functional symptoms, QRS duration, LVEF, left ventricle telediastolic diameter and any aggravation or onset of ventricular arrhythmia before and after biventricular resynchronization. Biventricular resynchronization led to an improvement in dyspnea in 80% of cases (one or more class decrease on NYHA scale), a significant shortening in QRS duration (−40 ms, \( p < 0.05 \)), a significant improvement in left ventricular dilation (−4 mm, \( p < 0.05 \)) and a significant improvement in the ejection fraction (4%, \( p < 0.05 \)). This study showed that in paced patients presenting with cardiac failure and systolic dysfunction refractory to medical treatment, upgrading from a conventional pacing system to a biventricular pacemaker leads to a significant improvement in functional symptoms.

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Résumé La resynchronisation biventriculaire a démontré son bénéfice en termes de morbidité et de mortalité chez les patients en insuffisance cardiaque systolique (fraction d’éjection ventriculaire gauche [FEVG] inférieure ou égale à 35 %) symptomatique (cla***s III et IV de la NYHA) sous traitement médical optimal avec asynchronisme électrique (QRS ≥ 120 ms) et en rythme sinusal. Notre travail vise à évaluer l’efficacité et la tolérance de la resynchronisation biventriculaire chez les patients déjà implantés d’un pacemaker en prés***ant une insuffisance cardiaque systolique symptomatique. Sur une période de huit ans, 24 patients déjà implantés d’un pacemaker en insuffisance cardiaque systolique (FEVG ≤ 35 %) symptomatique (cla***s III et IV) avec asynchronisme électrique (QRS ≥ 140 ms) ont bénéficié de l’implantation d’une sonde de stimulation ventriculaire gauche avec changement concomitant de leur boîtier. Nous avons comparé la symptomatologie fonctionnelle, la durée du QRS, la FEVG, le diamètre telédiastolique du ventricule gauche et l’aggravation éventuelle ou l’apparition d’arythmie ventriculaire avant et après resynchronisation biventriculaire. La stimulation biventriculaire s’accompagne d’une amélioration de la dyspnée dans 80 % des cas (diminution d’un stade ou plus de la NYHA), d’un raccourcissement significatif de la durée du QRS (−40 ms, p < 0,05), d’une régression significative de la dilatation ventriculaire gauche (−4 mm, p < 0,05) et d’une amélioration significative de la fraction d’éjection (+4 %, p < 0,05). Cette étude montre que chez les patients déjà implantés d’un stimulateur cardiaque et présentant une insuffisance cardiaque avec dysfonction systolique et rebelle au traitement médical, la resynchronisation entraîne une amélioration significative de la symptomatologie fonctionnelle.
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Introduction

The Multisite Stimulation in Cardiac insufficiency (Mustic) [1], Multicenter Insync Randomized Clinical Evaluation (Miracle) [2] and Cardiac Resynchronization in Heart Failure (CARE-HF) [3] clinical trials have shown that, in patients presenting with symptomatic heart failure (NYHA class III and IV) with left systolic ventricular dysfunction (left ventricular ejection fraction [LVEF] greater or equal to 35%), electrical asynchrony (QRS ≥ 120 ms) and sinus rhythm, cardiac pacing with biventricular resynchronization yielded significant benefits in terms of alleviation of symptoms (dyspnea) [1,2], and above all in overall mortality [3] in comparison to patients receiving optimal pharmacological treatment only.

The populations enrolled in these different studies did not include previously paced patients receiving permanent right ventricular stimulation, although this type of stimulation can induce or exacerbate interventricular asynchronism [4]. Thus, in patients presenting with left ventricular dysfunction, right ventricle stimulation can alter both diastolic and systolic ventricular function. This was recently confirmed by the David study [5], which showed that the risks of hemodynamic deterioration and mortality were higher in heart failure patients receiving traditional cardiac stimulation.

The aim of this study is to evaluate the functional efficacy and safety of biventricular resynchronization in previously paced patients.

Methods

Study

The objective of this single-centre, retrospective study was to evaluate the effects of ventricular resynchronization in patients, who received a pacemaker for a conventional cardiac stimulation indication, and who had subsequently undergone biventricular resynchronization in addition to this conventional stimulation.

Inclusion criteria

The inclusion criteria were as follows:
- symptomatic cardiac failure (NYHA class III–IV) despite medical treatment including at least two of the three following types of medicinal product at their optimal doses (individual tolerance) for each patient:
  - diuretic,
  - ACE-inhibitors,
  - beta blockers;
- LVEF ≤ 35%,
- right ventricular paced-dependent patients;
- ventricular asynchronism defined by electrical asynchrony defined as a QRS width greater or equal to 160 ms.

Exclusion criteria

Patients were excluded from this study for the following reasons:
- hypertrophic or restrictive cardiomyopathy;
- acute myocarditis;
- history of acute coronary syndrome in the three months preceding biventricular resynchronization;
- arterial hypertension refractory to medical treatment;
- history of cardiogenic shock in the week prior implantation;
- non-dependent paced patients.

Biventricular stimulation programming

Biventricular resynchronization was achieved by implanting a left ventricular lead in the coronary sinus via a lateral or postero-lateral coronary vein. Any patients in sinus rhythm
Resynchronization and pacemaker

with a dual chamber pacemaker had their device replaced with a conventional triple chamber pacemaker and the right-ventricle-left ventricle interval was set, whenever possible, at the nominal value (0 ms). In the event of chronic atrial fibrillation, a conventional dual chamber pacemaker was used with the left ventricular lead connected in the atrial channel and the right ventricular lead connected in the ventricular channel. In such patients, the atrioventricular interval was set at its minimum value (< 20 ms) so that the two ventricles were stimulated in a synchronized fashion (LV 20 ms ahead of RV) without recourse to cardiac ultrasound programming.

Evaluation of patients

The patients were assessed both before and after biventricular resynchronization (with no minimum or maximum interval after resynchronization) on the basis of the five following criteria:

- the primary assessment criterion was the functional symptoms;
- duration of QRS before and after resynchronization, and thus changes in QRS width;
- LVEF evaluated by cardiac ultrasound;
- left ventricular telediastolic diameter evaluated by cardiac ultrasound;
- onset or aggravation of ventricular arrhythmias and mortality at the time the data were collected in May 2007.

Statistical analysis

Data analysis consisted of:

- a description of the characteristics of the study population. The qualitative variables were described by percentages, and the quantitative variables by the mean, standard deviation and minimum and maximum values;
- and a comparison of the parameters recorded before and after resynchronization via a $t$-test for paired series. The alpha risk was set at 5%.

Statistical analyses were performed using SAS v9.1 software.

Results

Description of the study population

A total of 24 patients were included in the study with a mean follow-up time of 26 months (range: 1–108 months). Details of the population are provided in Table 1. There were 19 men and five women with a mean age of 75 ± 8 years (range: 52–86). All patients presented with severe cardiac failure with grade III and IV dyspnea in 83% and 17% of cases, respectively.

Over half of the patients (13/24) were in sinus rhythm while the remaining 11 (46%) were in permanent atrial fibrillation (AF). Of these 11 patients, four had undergone His bundle ablation. LVEF was 27 ± 6% (ranging from 15 to 35).

ACE-inhibitors and/or angiotensin II receptor antagonists were prescribed in 100%, beta-blockers in 83%, diuretics in 91%, digitalis in 13% and anti aldosterones in 30% of patients.

Effects of biventricular pacing

The effects of biventricular pacing on the primary and secondary endpoints are summarized in Tables 2a and 2b.

Primary assessment criterion

Biventricular resynchronization led to an improvement in functional status with a decrease of one or two NYHA class in 20 out of the 24 patients (80%).

Secondary assessment criteria

QRS duration was shortened by a mean of 40 ms (standard deviation of 20 ms), decreasing from 180 ms before resynchronization to 140 ms afterwards ($p < 0.0001$) with a mean concomitant reduction in left ventricular diastolic diameter of 4 mm (standard deviation of 7 mm) ($p = 0.02$) and a 4% increase in LVEF (standard deviation of 9%) ($p = 0.045$).

During the follow-up period, four patients exhibited ventricular arrhythmias, i.e., ventricular premature beats in two, ventricular tachycardia (VT) in one, VT which was well tolerated and resolved spontaneously and well tolerated slow VT mimicking an accelerated idiopathic ventricular rhythm in one. These two VT episodes were retrieved from the pacemaker Holter memories. Three of these four patients did not present with any improvement in their LVEF during follow-up.

Mortality

Four patients died during follow-up: two from unrecorded causes, one from mechanical valve thrombosis related to inappropriate anticoagulation therapy, and one from refrac-

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>%</th>
<th>Mean (standard deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>19</td>
<td>79</td>
<td>75 (8)</td>
</tr>
<tr>
<td>Men</td>
<td>20</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>NYHA III</td>
<td>4</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>NYHA IV</td>
<td>11</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Rhythm</td>
<td>13</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Sinus</td>
<td>11</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td>4</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>HIS ablation</td>
<td>4</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td>27</td>
<td>27% (6)</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors and/or ARA II</td>
<td>24</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>22</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Betablockers</td>
<td>20</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Digitalis</td>
<td>3</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Anti-aldosterone</td>
<td>7</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

ARA II: angiotensin II receptor antagonist; AF: atrial fibrillation; LVEF: left ventricular ejection fraction; HIS: bundle of HIS; ACE inhibitors: angiotensin-converting enzyme inhibitors.
tory heart failure. The intervals between implantation and death were seven, eight, five and seven years respectively.

Discussion

This retrospective study evaluating the effects of biventricular resynchronization in patients previously implanted with a pacemaker for a conventional indication and presenting with symptomatic refractory heart failure and electrical asynchrony, shows that adding a left ventricular lead is associated with a functional improvement. In these patients, biventricular resynchronization significantly reduced the QRS duration and the left ventricular end diastolic diameter. It also led to a significant increase in the left ventricular ejection fraction. These positive results should be offset against the onset or exacerbation of ventricular arrhythmias in 20% of cases, although these were well tolerated.

The Mustic and Miracle studies had already demonstrated the benefits of biventricular resynchronization on functional criteria. The positive effects of resynchronization have since been confirmed in numerous studies. Bradley’s meta-analysis [6] evidenced a 30% decrease in the number of hospitalizations for cardiac failure after implantation of a multisite pacemaker. The positive impact on the number of hospitalizations for heart failure tends to indicate that resynchronization could be of major medical-economic value since hospitalizations for heart failure are believed to represent 60% of the expenditure related to this condition [7].

Recently, the CARE HF study showed that atrio-biventricular resynchronization also led to reduced mortality in comparison to optimal medical treatment. However, all the paced patients enrolled in these studies were in sinus rhythm and one of the inclusion criteria was the absence of a pre-existing pacemaker and/or absence of an indication for permanent cardiac pacing.

The RD-CHF study [8] was the first randomized, prospective study with a cross-over design to assess the effects of biventricular resynchronization in permanently paced patients. The 56 patients enrolled in this single-center study presented with advanced, symptomatic heart failure (NYHA class III and IV) under optimal medical therapy, and mechanical asynchrony evidenced on the cardiac ultrasound examination. Three months of right ventricular stimulation alone were compared with three months of biventricular stimulation (cross-over after three months). The results showed an improvement in the functional symptoms and signs of heart failure, a reduction in QRS duration and above all a decrease in the number of patients requiring hospitalization for heart failure with biventricular pacing as compared to permanent right ventricular pacing alone. These results match the findings of our study, with the exception of the decrease in hospitalizations which was not evaluated in this study.

The benefits of resynchronization in paced patients were also evidenced in the study conducted by Eldadah et al. [9] who used tissue Doppler and strain rate imaging to assess left ventricular systolic function in 12 patients as well as in the study by Marai et al. [10]. In the Marai study, 98 patients with refractory heart failure were divided into two groups: 25 patients with right ventricular apical pacing were upgraded to cardiac resynchronization therapy and 73 patients received de novo resynchronization therapy. The benefits of resynchronization were at least equal in the two groups. Finally, a recent study by Laurenzi et al. [11] confirmed the benefits of biventricular upgrading in patients with a conventional pacing system in terms of improvement in symptoms and inverse remodeling.

Almost half the patients enrolled in this study presented with permanent AF. Data on biventricular resynchronization for AF are limited. The Mustic AF study enrolled 48 patients with permanent AF and slow ventricular conduction and compared right ventricular apical pacing (VVIR mode) to biventricular pacing (BIV VVIR). An improvement in functional symptoms was observed after upgrading to biventricular pacing versus conventional pacing. The mean six minute walk distance was increased by 32 meters ($p < 0.05$) and a 13% increase in the $V_{O_{2\text{max}}}$ peak ($p < 0.05$) was also observed. On the other hand, biventricular pacing was not

<table>
<thead>
<tr>
<th>Parameters Before mean (S.D.)</th>
<th>After mean (S.D.)</th>
<th>Before-after mean (S.D.)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{O_{2\text{max}}}$</td>
<td>15 (3)</td>
<td>17 (6)</td>
<td>−4.4 (2)</td>
</tr>
<tr>
<td>LVTD</td>
<td>68 (11)</td>
<td>64 (9)</td>
<td>4.6 (7)</td>
</tr>
<tr>
<td>QRS duration</td>
<td>0.18 (0.04)</td>
<td>0.14 (0.03)</td>
<td>−0.04 (0.02)</td>
</tr>
<tr>
<td>LVEF</td>
<td>27 (7)</td>
<td>31 (11)</td>
<td>−4.3 (9)</td>
</tr>
</tbody>
</table>

LVTD: left ventricular telediastolic dilation; LVEF: left ventricular ejection fraction; $p$: degree of significance; S.D.: standard deviation; $V_{O_{2\text{max}}}$: maximum oxygen consumption.
correlated with a decrease in the number of hospitalizations or in mortality. The findings of the Mustic AF study were further confirmed by the Pave study [12] which compared biventricular resynchronization to right ventricular pacing alone in patients who had undergone His-bundle for rapid permanent atrial fibrillation. Like in the Mustic AF study, the Pave study demonstrated a functional improvement in the biventricular group.

In this study, resynchronization was associated with the onset of ventricular arrhythmias in four patients. This deleterious effect of resynchronization on heart rhythm was not reported in the RD-CHF [8] or Contak CD [13] studies. A possible explanation for this difference could be the lack of any improvement in the LVEF which remained below 30% after resynchronization in three out of four patients who developed ventricular arrhythmias. Rather than a deleterious effect of resynchronization, this phenomenon could be explained by the natural progression of left ventricular dysfunction in non responding patients.

**Study limitations**

There are several limitations in this study. In addition to its retrospective and non comparative design, there is a selection bias, since only patients in whom resynchronization was possible were included. In addition, the statistical power of the study is reduced due to the small study population. Its retrospective nature highlighted the fact that data were incomplete for some patients. Finally, it would have been interesting to perform a sub-group analysis in patients who had undergone His-bundle ablation for permanent atrial fibrillation. This was not impossible due to the small number of patients enrolled.

**Conclusion**

Despite its limitations, this study shows that in previously paced patients presenting with heart failure-refractory to optimal medical treatment and decrease left ventricular function upgrading to biventricular pacing is associated with an improvement in functional symptoms. This positive effect of resynchronisation is not only obtained in patients who are in sinus rhythm but also in AF patients. It can therefore be proposed as an effective therapeutic option for the treatment of this type of patient.

**References**